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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/674,092	08/26/2002	Marcus Keep	30-200P	1549

2292 7590 11/16/2007
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EXAMINER	
MOHAMED, ABDEL A	
ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
11/16/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	09/674,092	KEEP ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 21-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 21-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

ACKNOWLEDGMENT TO AMENDMENT, REMARKS AND STATUS OF THE CLAIMS

1. The amendment and remarks filed 09/05/07 are acknowledged, entered and considered. In view of Applicant's request claims 1, 21 and 22 have been amended and claims 24-26 have been added. Claims 1-14 and 21-26 are now pending in the application. The rejections under 35 U.S.C. 112, first paragraph and 35 U.S.C. 103(a) over the prior art of record are withdrawn in view of Applicant's amendment and remarks filed 09/05/07. The rejection under 35 U.S.C. 103(a) over the prior art of record has been considered but deemed to be moot in view of the new ground of rejections as set forth *infra*.

NEW GROUND OF REJECTION

CLAIMS REJECTION-35 U.S.C. § 103(a)

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-14 and 21-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kaswan (U.S. Patent No. 4,649,047) taken with Elzinga et al (Transplantation, Vol. 47, No. 2, pp. 394-395, February 1989), Broadwell et al (Science, Vol. 217, No. 4555, pp. 164-166, July 9, 1982), Elias (U.S. Patent No. 5,807,820) and Okonkwo et al (J. Cereb. Blood Flow Metab., Vol. 19, No. 4, pp. 443-451, 1999).

The primary reference of Kaswan ('047 patent) discloses a pharmaceutical composition comprising cyclosporin such as cyclosporin A (CsA) in a concentration of 0.1 to 20 wt% of cyclosporin dissolved in medically suitable excipients, preferably dimethyl sulfoxide (DMSO), and since the concentration of cyclosporin is from 0.1 to 20% by weight, the rest is excipient which must be at least 80% by weight of the pharmaceutical composition which is administered topically to the eyes i.e., intra-ocular administration (See e.g., abstract; col. 6, lines 21 to 60; Example 2; claims 3, 4, 7, 8 and 13-16) as directed to claims 1, 2 and 6.

The primary reference of '047 patent differs from claims 1-14 and 21-26 in not teaching a) administering a pharmaceutical composition comprising DMSO and cyclosporin by injection into cerebrospinal fluid or cerebrospinal spaces of a patient as

claimed in claim 3, or intravestibularly, as recited in claim 4, b) administering the pharmaceutical composition according to claim 1 by injection intravenously, intra-arterially or intraparenchymally, as recited in claim 5, or inhalationally or nasally, as recited in claim 6, c) disclosing an article of manufacture as recited in claim 8, d) disclosing a method of treating any and all of the diseases recited in claim 11, and e) disclosing a method fro inducing systemic immunosuppression in patients of transplantation or autoimmune disease (claim 12).

However, the secondary reference of Elzinga et al compares the effect of DMSO with that of the conventional olive oil vehicle on the absorption of cyclosporin following oral administration in rats. The reference states that following oral administration of CsA solution, the absorption of CsA is highly variable and incomplete, ranging from 4% to 26% of the administered dosage in one study in renal transplant recipients. Nevertheless, DMSO is an excellent organic solvent that readily penetrates most tissue membranes, acting as a "carrier" for many solutes, including various drugs. Thus, the reference clearly shows that DMSO penetrates most biological membranes with ease, and has been used as an effective carrier of drugs and other solutes and considered to be safe. The reference of Elzinga concludes by stating that the increased bioavailability of CsA following administration in DMSO is due to enhanced gastrointestinal absorption, although other effects of DMSO on CsA pharmacokinetics cannot be excluded. Complete pharmacokinetic and immunosuppression studies in humans are warranted as the use of DMSO as the vehicle for CsA could result in considerable cost savings, provided immunosuppression is not compromised (See e.g., pages 394 and 395).

Further, the secondary reference of Broadwell et al describes the morphologic effect of DMSO on blood-brain barrier. Although, the use of DMSO in the treatment of cerebral infarction, brain swelling, and spinal cord injury is controversial, however, morphological changes were observed on gross or microscopic in brain parenchyma from mice exposed to DMSO concentration of up to 15%. Brains and pituitaries from animals given 0.5 ml of DMSO intraperitoneally and 0.25 ml of DMSO intravenously at concentrations up to 15% did not exhibit hemorrhage. Although, claims 1 and 21 as amended recite at least 80% of DMSO by weight in the composition, the reference of Broadwell clearly states that regardless of the volume, concentration and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver, and intestines of all DMSO injected mice appeared normal on gross examination at autopsy. Thus, the reference of Broadwell et al concludes by stating that the search of a safe and reliable approach for promoting the entry to the brain of blood-borne chemotherapeutic agents and antibiotics may depend on an increased understanding of the mechanism of blood-brain barrier function. Whether or not DMSO can safely and effectively open the blood-brain barrier *in vivo* to chemotherapeutic drugs and antibiotics requires further investigation.

Therefore, in view of the above, the secondary reference clearly motivates one of ordinary skill in the art at the time the invention was made to use DMSO as a carrier in any drug of choice because as stated above regardless of the volume, concentration and route of delivery of DMSO, the corneas, lungs, heart, kidneys, liver, and intestines of all DMSO injected mice appeared normal on gross examination at autopsy (See e.g., pages 164 and 165). Furthermore, the reference of Elias discloses pharmaceutical

compositions comprising cyclosporin wherein the cyclosporin is CsA having a concentration from 0.1 to 50% of a cyclosporin based on total weight and useful for topical application (See e.g., col. 9, line 36-37 and claims 1 and 2). Thus, the secondary references clearly show the use of DMSO as a carrier/penetrating agent in a medicinal formulation wherein the medicinal agent or formulation could be the combination of DMSO and any agent of interest, which may include cyclosporins, particularly CsA at claimed concentrations.

Moreover, the secondary reference of Okonkwo et al discloses the use of an intrathecal bolus of CsA before injury preserved mitochondrial integrity and attenuated axon disruption in traumatic brain injury. Pretreatment with CsA significantly reduced the number of axons undergoing delayed axotomy, as evidenced by a decrease in the density of amyloid precursor protein-immunoreactive axons. Collectively, the study demonstrated that CsA protects both mitochondria and the related axonal shaft, suggesting that this agent (i.e., CsA) may be of therapeutic use in traumatic brain injury (See e.g., abstract and the title). Thus, clearly showing introduction of CsA into the cerebrospinal compartments of a subject, and as such meet the limitations of claim 3, 4 and dependents thereof.

Therefore, in view of the above and in view of the combined teachings of the prior art, it would have been routine and conventional to one of ordinary skill in the art to which this invention pertains to administer a pharmaceutical formulation of interest to a patient in need thereof. Because the appropriate dosages and modes of administration can and will be determined by the prescribing physician and will be a result of the

severity of the condition being treated as well as the response with the derivatives being administered and the age, weight, sex and medical history of the patient.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have combined the teachings of the primary reference of Kaswan or the reference of Elzinga et al with the reference of Broadwell et al or Elias or Okonkwo et al in order to administer cyclosporin and DMSO by any one of the modes of administration and dosages thereof recited in claims 3-6, 10, 13, 14, 21, 22 and 24-26. The artisan of ordinary skill in the art utilizing the methods of Broadwell et al would have obtained the improvement when such combinations and formulations (as disclosed in the primary reference) are administered to patients suffering from the diseases or conditions recited in claims 11 and 12. Further, such features (i.e., using DMSO as a carrier on blood-brain barrier) are known or suggested in the art, as seen in the secondary references, and including such features into the composition of the primary reference of '047 patent would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

In regard to claims 8 and 9, an article of manufacture comprising packaging material and pharmaceutical agent or formulation claimed for the intended purposes for reducing or treating neuronal damage and for causing immunosuppression when administered; but, where the above reference differs from claims 8 and 9 in not teaching *per se* the formulation claimed in a packaging material and use thereof. However, it would have been obvious to package the composition required for the method into

packaging material and/or kit format of the well-known commercial expediency of dong so.

Therefore, in view of the above, in view of the combined teachings of the prior art, and in the absence of unexpected results or factual evidence to the contrary, modification such as the selection of an appropriate cyclosporin and formulations of packaging material and/or kit thereof, as well as the selection of optimum and/or appropriate concentrations of cyclosporin and DMSO, mode of administration and dosages thereof is within the purview of one of ordinary skill in the art to which this invention pertains, and as such would have resulted in the claimed invention which was *prima facie* obvious to make and use at the time it was made.

CONCLUSION AND FUTURE CORRESPONDANCE

3. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tsang Cecilia can be reached on (571) 272 0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JON WEBER
SUPERVISORY PATENT EXAMINER

Mohamed/AAM
October 31, 2007